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# (54) Pharmaceutical compositions containing ubiquinones

(57) Pharmaceutical compositions comprising combinations of an ubiquinone and dry yeast extract, having a synergetic effect, useful in the treatment of muscular fatigue, senescence or diseases connected to impaired intestinal biochemism. Coenzyme $Q_{10}$ is the preferred ubiquinone and brewers' yeast extract, free from bitter substances the preferred yeast.

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SPECIFICATION

## Pharmaceutical composition

The present invention relates to pharmaceutical compositions having tissular metabolic activity intended for oral administration.

Brewers' yeast dried and freed from its bitter substances is a natural source of essential aminoacids and vitamins of complex B. Generally, 1 g of yeast contains about 40% proteins, 0.12 mg thiamine hydrochloride, 0.04 mg riboflavine, 0.25 mg nicotinic acid, pyridoxine and pantothetic acid. It contains also a number of enzymes (zymase, sucrase, maltase, etc.) and nucleins, peptone and also many fatty compounds, particularly ceroline.

A characteristic of brewers' yeast is to make easily usable by the body the vitamin complexes contained therein, as well as to supply a series of enzymes which are necessary to intestinal biochemistry. The presence of enzymes and complex B vitamins leads, in case of a deficiency thereof, to an activation of glycolytic processes and to a higher energetic supply to cells and tissues.

ATP production is based on glycolytic processes and oxidative phosphorylation, but is also should be taken into account that oxygen utilization as well as energy production at the mitochondria level depend on the presence of Coenzyme $Q_{10}$.

Coenzyme $Q_{10}$ is biochemically known to be a redox component of the respiratory chain and of the oxidative phosphorylation mechanism related thereto. Coenzyme $Q_{10}$ plays an essential role in the mitochondrial electron transport between flavoprotein and cytochrome systems in ATP production. A lack in Coenzyme $Q_{10}$, as well as a deficiency in the enzymatic systems connected to glycolysis and oxidative phosphorylation, such as those depending on complex B vitamins, has been shown in different pathological conditions, mainly in muscular energetic systems.

These conditions mainly take place in senescence, atherosclerosis, myocardiac insufficiency, poor cerebal vascularization and in case of increased energetic requirements, such as during growth, muscular efforts, etc.

Under all these conditions, and exogenous contribution in natural vitamin B complex and Coenzyme $Q_{10}$ proved to be useful (Folkers K. et al., IV Int. Symp. on the Biomedical and Clinical Aspects of Coenzyme Q, Munich 1983), as has been shown in recent evidence (Mortensen S.A. et al., Drugs Exptl. Clin. Res. 1984; Folkers K. et al., Internal. J. Vit Res. 40-380-1970).

Whilst therapeutic uses of vitamin B complex as well as of yeast are well known, the healing action of Coenzyme $_{10}$, particularly in myocardial insufficiency, hypertension and post-infarction conditions and its action favouring energetic muscular performances has been shown only recently (Biomedical and Clincal Aspects of Coenzyme Q–Folkers K., Yamamura G. Editors–Vol. 3–Elsevier/North Holland Biomedical Press 1981).

Besides intervening in the above biochemical interactions, brewers' yeast can supply those amino acids, fatty substances and enzymes favouring the Coenzyme $Q_{10}$ absorption by the intestinal tract and the biosynthesis thereof.

Coenzyme $Q_{10}$ liposolubility and the role of such amino acids as tyrosine in the biosynthesis thereof are in fact known, as well as the difficulties in obtaining an efficient absorption of Coenzyme $Q_{10}$ by the oral route.

Brewers' yeast, besides containing, among the other amino acids, tyrosine, is also rich in vitamins and fatty substances.

The present invention relates to pharmaceutical compositions having tissular metabolic activity, for oral administration, containing a coenzyme selected from the ubiquinone series (Coenzyme Q for 1 to 10), more particularly Coenzyme $Q_{10}$, and dry brewers' yeast extract.

The combination of ubiquinone enzyme, e.g. Coenzyme $Q_{10}$, with yeast extract showed surprisingly a synergetic effect on metabolic and energetic activities carried out by Coenzyme $Q_{10}$ as well as on its absorption in the intestine.

In fact, a surprising synergetic activity between yeast extract and Coenzyme $Q_{10}$ was shown both in the adaptation to the prolonged muscular effort and in protecting myocardium from toxic effects of anoxia, and in increasing hematic and tissular concentration of Conenzyme $Q_{10}$.

The pharmaceutical compositions of the invention, containing a combination of ubiquinone enzyme, e.g. Coenzyme $Q_{10}$, and yeast extract, allow one therefore to obtain unexpected pharmacological and therapeutic effects, due to a synergetic action which could not be foreseen on the bases of the data hitherto known, and wich in any case could not be obtain d from th simple addition of the effects of th single c mponents.

The validity of the present inv nti n, in any cas , does not depend on the exactn ss of the above mentioned biologic mechanisms.

*Toxicology and pharmacology*

The poor toxicity and good tolerability of Coenzyme $Q_{10}$ and dry yeast extract are well-known.

Tests carried out in order to valuate if the $LD_{50}$ for Coenzyme $Q_{10}$, by the oral route would be aff cted by the administration of yeast extract and vice-v rsa, could ascertain no chang s, even when orally administering to the rat and the mouse dosages higher than 5 kg/mg of 1:2 mixture of the two compounds.

Also chronic toxicity tests carried out in the rat, orally administering 1g/kg of a mixture of the two compounds in 1:1 – 1:20 – 1:100 ratios for 3 consecutive months, gave no evidence of a toxic effect nor intolerance symptoms on body weight and the different hemochromocytometric or hematochemical parameters.

*Tests on oral adsorption of Coenzyme $Q_{10}$*

In these tests, oral absorption of Coenzyme $Q_{10}$ alone or combined with dry yeast extract was measured. The test were carried out in male Wistar rats, fasted for 12 hours, and the measurement of Coenzyme $Q_{10}$ concentrations was carried out in blood, heart, liver and kidneys at times varying from 0.5 to 8 hours after administration. The dosage was measured by gas chromatography, according to Abe. K. et al (Proc. Int. Symp. Boimedical and Clinical Aspects of Coenzyme $Q_{10}$, Austin Gen. 1981). The result reported in Table 1 show that the combination of dry brewers' yeast extract and Coenzyme $Q_{10}$ surprisingly improves oral absorption of Coenzyme $Q_{10}$. Both hematic and tissular concentrations of Coenzyme $Q_{10}$ in the group of animals treated with the combination according to the invention were surprisingly higher than those measured in the group of animals which received Coenzyme $Q_{10}$ alone.

*Tests on muscular exercise*

Training involving muscular exercise and higher resistance to fatigue are related to an increase in mitochondrial enzymes activity. The test were carried out on groups of Spraque-Dawley male rats, one group of which was the control group, another one of which was subjected to muscular exercise for 7 or 30 days, whilst other groups were subjected to muscular exercise for 7 or 25 days, together with a daily oral treatment with 10 g/kg Coenzyme $Q_{10}$, or with 2.5 g/kg dry yeast or with the combination of the invention, at the same dosages. Muscular exercise was performed by means of a Rotarod device, 20 m/min. for 120 minutes-daily. 7 or 25 days after commencement, the animals were killed, the gastrocnemius muscle thereof was isolated, homogenized and subject to differential centrifugation to measure mitochondrial enzymatic activity at the spectrophotometer, according to Oscai L.B. et al. (J. Biol. Chem. 246-6968-1971).

The results of Table 2 show that the treatment with Coenzyme $Q_{10}$ and brewers' yeast, already after 7 days of muscular exercise and even more after 30 days. leads to a surprisingly higher increase in mitochondrial enzymatic activity than that shown when administering Coenzyme $Q_{10}$ or dry yeast alone, or foreseeable from the simple addition of the two effects.

*Tests on myocardiac anoxia*

In these tests myocardiac anoxic conditions were induced by intravenous injection of 1 unit/kg pitressin in the rat. The coronary spasm induced by pitressin leads to a decreased myocardiac oxygenation and to the appearance of typical asphyxia T waves in the electrocardiogram. A selected group of male Wistar rats was previously orally administered with 5 g/kg or 1g/kg Coenzyme $Q_{10}$, each day for 7 consecutive days. Another group received the two compounds combined. After 7 days of treatment, the injection of pitressin caused the appearance of asphyxia T waves, which were unchanged in the group treated with only yeast, and reduced by about 50% in the group treated with Coenzyme $Q_{10}$ alone, whilst said waves nearly did not appear in the group treated with the combination of Coenzyme $Q_{10}$ with yeast. A strong synergetic effect for the components of the combination was thus shown also in this test.

TABLE 1 - Hematic and tissular concentrations of Coenzyme $Q_{10}$ (100 mg/kg orally administered to the rat, alone or combined with dry brewers' yeast (2.5 g/kg).
The values are expressed in mcg/ml or mcg/g.
A = Coenzyme $Q_{10}$ administered alone.
B = Coenzyme $Q_{10}$ administered with dry yeast extract.

| | TIME FROM THE ADMINISTRATION (in min.) | | | | | |
|---|---|---|---|---|---|---|
| | 0 | 30 | 60 | 120 | 180 | 360 |
| Plasma A | - | 0.10 | 0.320 | 0.815 | 0.980 | 0.920 |
| B | - | 0.25 | 0.525 | 1.114 | 1.730 | 1.600 |
| Kidney A | 14.80 | 18.63 | 18.85 | 19.15 | 15.70 | 15.90 |
| B | 14.22 | 20.55 | 22.60 | 20.18 | 18.60 | 18.25 |
| Liver A | 10.40 | 11.60 | 13.15 | 20.65 | 22.85 | 20.15 |
| B | 10.75 | 12.50 | 14.70 | 27.10 | 30.95 | 30.70 |
| Heart A | 12.15 | 14.22 | 14.85 | 13.40 | 12.75 | 12.50 |
| B | 12.55 | 18.40 | 19.62 | 16.85 | 14.29 | 13.22 |

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TABLE 2

| Treatment | Days of exercise | (*) Citrate synthetase | Isocitrate dehydrogenase | Succinate dehydrogenase |
|---|---|---|---|---|
| Controls | No exercise | 20.2±1.7 | 2.22±0.16 | 3.15±0.19 |
| Controls | 7 | 21.4±1.9 | 2.40±0.19 | 3.56±0.13 |
| Controls | 30 | 30.7±2.1 | 3.75±0.11 | 5.05±0.20 |
| Coenzyme $Q_{10}$ 10 mg/kg | No exercise | 22.4±2.9 | 2.70±0.15 | 3.80±0.17 |
| Coenzyme $Q_{10}$ 10 mg/kg | 7 | 36.4±3.1 | 3.55±0.21 | 5.15±0.21 |
| Dry yeast extract 500 mg/kg | No exercise | 19.9±2.3 | 2.40±0.20 | 3.20±0.23 |
| Dry yeast extract 500 mg/kg | 7 | 21.7±1.8 | 3.90±0.18 | 3.85±0.22 |
| Coenzyme $Q_{10}$ 10 mg/kg + dry yeast extract 500 mg/kg | No exercise | 27.2±1.9 | 2.90±0.23 | 3.90±0.20 |
| Coenzyme $Q_{10}$ 10 mg/kg + dry yeast extract 500 mg/kg | 7 | 40.1±1.7 | 5.2±0.25 | 6.64±0.30 |

(*) Enzymatic activities are expressed as μm of substrate used per minute/g of weight.

A main aspect of this invention relates to the prophylactic and therapeutic application of the combination of Coenzyme $Q_{10}$ with yeast.

The present invention relates to pharmaceutical compositions containing Coenzyme Q, preferably Coenzyme $Q_{10}$, and brewers' dry yeast, suitably in a ratio ranging from 1:1 and 1:10,000, optionally added with vitamins of Group B or other vitamins or salts, and conventional excipients.

Non-limiting examples of pharmaceutical compositions formulated according to conventional pharmaceutical techniques are the following:

*Tablets or capsules containing:*

Coenzyme $Q_{10}$ 0.1 mg+Brewers' yeast dry extract 150mg
Coenzyme $Q_{10}$ 1 mg+Brewers' yeast dry extract 300 mg
Coenzyme $Q_{10}$ 5 mg+Brewers' yeast dry extract 300 mg
Coenzyme $Q_{10}$ 50 mg+Brewers' yeast dry extract 300 mg
Coenzyme $Q_{10}$ 100 mg+Brewers' yeast dry extract 300 mg

*Vials of syrup and/or granulate*

Coenzyme $Q_{10}$ 1 mg+Brewers' yeast dry extract 200 mg
+ Vit. $B_1$ 0.01 mg
Vit. $B_2$ 0.05 mg
Vit. $B_6$ 0.05 mg
Vit. $B_{12}$ 0.01 mg
Mineral salts

or Coenzyme $Q_{10}$ 5 mg+Brewers' yeast dry extract dry extract 200 mg
+Vit. $B_1$ 0.01 mg
Vit. $B_2$ 0.05 mg
Vit. $B_6$ 0.05 mg
Vit $B_{12}$ 0.01 mg

or Coenzyme $Q_{10}$ 10 mg+Brewers' yeast dry extract 200 mg
+Vit. $B_1$ 5 mg
Vit. $B_2$ 5 mg
Vit. $B_6$ 10 mg
Vit. $B_{12}$ 0.5 mg
Vit. A 500 U.I.
Vit. E 5 mg
Vit. C 100 U.I.
Vit. D 100 U.I.

CLAIMS

1. A pharmaceutical composition having tissular metabolic activity, intended for oral administration, comprising a coenzyme selected from the ubiquinone series (Coenzyme Q from 1 to 10) or a mixture thereof, and dry yeast extract.

2. A pharmaceutical composition as claimed in claim 1, wherein the ubiquinone is Coenzyme $Q_{10}$.

3. A pharmaceutical composition as claimed in claim 1 or 2, wherein the yeast extract is dry brewers' yeast extract, free from bitter substances.

4. A pharmaceutical composition as claimed in any one of claims 1 to 3, wherein the Coenzyme $Q_{10}$: dry yeast extract weight ratio is between 1:1 and 1:10,000.

5. A pharmaceutical composition as claimed in any one of claims 1 to 4, in solid semi-solid or liquid form, for oral administration in human and/or animal therapy, to improve oral adsorption of Coenzyme $Q_{10}$ and its metabolic activity in the case of muscular fatigue, tissular anoxia, senescene and/or is disorders related to an impaired intestinal biochemism.

6. A pharmaceutical composition as claimed in any one of claims 1 to 5, in the form of capsules, suger-coated pills, tablets, granulates, syrups or oral vials.

7. A method for improving oral Coenzyme $Q_{10}$ absorption and the metabolic activity thereof, by means of combination with dry yeast extract.

8. A pharmaceutical composition according to claim 1 substantially as described herein.

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